Gender disparities in acute coronary syndrome: a closing gap in the short-term outcome

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Abstract: AIMS The aim of the present study was to analyze gender disparities in a large cohort of acute coronary syndrome (ACS) patients from the Zurich Acute Coronary Syndrome (Z-ACS) Registry. METHODS Gender disparities in ACS were examined. The primary endpoint included in-hospital death rate, and the secondary endpoint major adverse cardiac and cerebrovascular events (MACCEs) at 30-day follow-up. Furthermore, independent predictors for MACCEs and death were identified. RESULTS In total, 2612 patients with ACS were identified. Out of these, 23% were women. The mean age was higher in women (68.6 ± 12.2; P < 0.001). Troponin-T on admission (1.33 ± 4.64 vs. 1.19 ± 3.04 g/l; P = 0.002) and N-terminal of the prohormone brain natriuretic peptide on admission (3456.2 ± 7286.7 vs. 1665.6 ± 4800.6 ng/l; P < 0.001) were higher in women compared with men. Single-vessel disease was more common in women (44.9 vs. 39.7%; P = 0.023) and, conversely, multivessel disease was more prevalent in male patients as compared with their female counterparts (59.4 vs. 54.4%; P = 0.029). At discharge, men were more likely prescribed statins (89.4 vs. 85.2%; P = 0.004). Overall mortality and MACCEs were similar for both genders. In women, peak creatine kinase and peak C-reactive protein emerged as independent predictors for MACCEs and SBP on admission, and maximal C-reactive protein and use of glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa) as strong independent predictors for in-hospital death. CONCLUSION The present results suggest a closing gap in short-term outcome and improvement in cardiac care between women and men. Nonetheless, differences in treatment strategies continue to exist, particularly pertaining to statin regimens at discharge, which might potentially have a powerful impact on long-term outcomes and gender disparities.

DOI: https://doi.org/10.2459/JCM.0000000000000248

Original article

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

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Aims **The aim of the present study was to analyze gender disparities in a large cohort of acute coronary syndrome (ACS) patients from the Zurich Acute Coronary Syndrome (Z-ACS) Registry.**

Methods **Gender disparities in ACS were examined. The primary endpoint included in-hospital death rate, and the secondary endpoint major adverse cardiac and cerebrovascular events (MACCEs) at 30-day follow-up. Furthermore, independent predictors for MACCEs and death were identified.**

Results **In total, 2612 patients with ACS were identified. Out of these, 23% were women. The mean age was higher in women (68.6 ± 12.2; $P<0.001$). Troponin-T on admission (1.33 ± 4.64 vs. 1.19 ± 3.04 μg/l; $P=0.002$) and N-terminal of the prohormone brain natriuretic peptide on admission (3456.2 ± 7286.7 vs. 1665.6 ± 4800.6 ng/l; $P<0.001$) were higher in women compared with men. Single-vessel disease was more common in women (44.9 vs. 39.7%; $P=0.023$) and, conversely, multivessel disease was more prevalent in male patients as compared with their female counterparts (59.4 vs. 54.4%; $P=0.029$). At discharge, men were more likely prescribed statins (89.4 vs. 85.2%; $P=0.004$). Overall mortality and MACCEs were similar for both genders. In women, peak creatine kinase and peak C-reactive protein emerged as independent predictors for MACCEs and SBP on admission, and maximal C-reactive protein and use of glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa) as strong independent predictors for in-hospital death.**

Conclusion **The present results suggest a closing gap in short-term outcome and improvement in cardiac care between women and men. Nonetheless, differences in treatment strategies continue to exist, particularly pertaining to statin regimens at discharge, which might potentially have a powerful impact on long-term outcomes and gender disparities.**

J Cardiovasc Med 2015, **16**:355–362

Keywords: acute coronary syndrome, gender medicine, short-term outcome

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Received 30 December 2013 **Revised** 2 November 2014
Accepted 4 November 2014

Introduction

In the realm of cardiovascular disease (CVD), women have been historically understudied, despite the fact that they are equally adversely affected as men. As such, the WHO estimates that women suffer about 3.3 million deaths annually due to myocardial infarction.[1] This is an astonishing finding, which has been on the rise, exceeding the number of deaths in men from CVD since 1984.[1] Moreover, there is an accumulating body of evidence that not only women are understudied in clinical trials; they are also underdiagnosed due to different symptoms upon presentation, and even under-treated on admission.[2–7] Underrepresentation of women was particularly stressed in the American Heart Association (AHA) prevention guidelines of CVD in women published in 2007.[8] These guidelines were based on a mere population of 30% women enrolled in the clinical trials, albeit they exhibit a similar prevalence of coronary artery disease (CAD) as men.[2] Likewise, women's enrollment in randomized clinical trials (RCTs) in European countries[9,10] remains minuscule overall, ranging between 16 and 25%.[10,11]

Recent findings from the INTERHEART Study[12] demonstrated that gender-related differences in cardiovascular risk factors included diabetes and hypertension as strong risk factors, specifically in women. Thus, there is an urgent need for international improvement in clinical trial enrollment, guidelines establishment and healthcare delivery in women as a vulnerable population. The current study therefore aimed to investigate gender-related differences in the clinical profile and treatment, as well as in-hospital outcomes in acute coronary syndrome (ACS) in a large cohort of patients.

Methods

Data collection

We included consecutive patients with the diagnosis of ACS at the University Hospital of Zurich, Switzerland

DOI:10.2459/JCM.0000000000000248

(USZ) from 2007 to 2012 who underwent coronary angiography. All patients enrolled in this registry were at least 18 years of age. ACS was classified as ST-segment myocardial infarction (STEMI), non-ST-segment myocardial infarction (NSTEMI) or unstable angina (UA) based on the classification by Thygesen *et al.*[13] Patient data were collected from the an in-hospital clinical electronic patient record system at the USZ. Data were analyzed regarding baseline characteristics, laboratory values, patients' cardiovascular medications on admission and discharge. CAD was defined as single-vessel disease (SVD) or multivessel disease (MVD), and the culprit lesion was categorized as left main artery, left anterior descending (LAD) artery, circumflex artery, right coronary artery or coronary artery bypass graft (CABG). Furthermore, we included the hemodynamic parameters such as blood pressure, heart rate, left ventricular end-diastolic pressure and left ventricular ejection fraction (LVEF) from the left ventricular angiogram if performed.

The study was performed on behalf of the Special Programme University Medicine (SPUM) and a quality control of patients with ACS at the USZ. The study cohort was in part shared with the Zurich Acute Coronary Syndrome Registry (Z-ACS) reported elsewhere.[14]

Short-term follow-up

In-hospital outcome was reviewed, and the primary endpoint comprised overall in-hospital death and the secondary endpoint included major adverse cardiac event (MACCE), which was defined as in-hospital death, non-fatal myocardial infarction, revascularization, CABG, stent thrombosis, as well as stroke at 30 days of follow-up. Myocardial infarction was defined as angina pectoris symptoms combined with elevated cardiac enzymes and typical ECG patterns for myocardial infarction. Stroke was present if reviewed independently by a neurologist and classified according to focal neurologic deficits lasting longer than 24 h with a clinically relevant lesion on brain scanning.

Statistical analysis

SPSS software (Version 20.0, Chicago, Illinois, USA) was applied for all statistical analysis. A P value less than 0.05 was defined as statistically significant. Normally distributed variables are presented as frequencies or proportions, or as mean with SD. All baseline characteristics, hemodynamics, medication and outcomes for the gender analysis were summarized using frequency tables with count and proportion for each category, or median and interquartile range (IQR), respectively. Median and IQR were used for non-Gaussian distribution that was tested by Shapiro–Wilk test.

Differences between groups were tested using chi-square or Fisher's exact test for nominal endpoints, or the Kruskal–Wallis tests for continuous endpoints. Survival analysis for male and female patients at 30-day follow-up was performed applying the Kaplan–Meier method for the combined endpoint of MACCE. The curves were analyzed using the log-rank sum test.

Univariate and multivariate nominal regression models and odds ratio (OR) were applied to identify independent predictors of in-hospital death and MACCE. Variables included in the model were selected in a stepwise forward-selection manner. Entry and retention sets with a P value of less than 0.05 indicated a significant difference. A variable's risk was expressed as an OR with corresponding 95% confidence interval (CI).

Results

Baseline characteristics

The baseline characteristics after stratification into two groups are shown in Tables 1–3. In total, 2612 patients were included in the present study. Out of these, 2011 (77%) patients were men and 601 (23%) were women. The average age was significantly higher in women as compared with men (68.6 ± 12.2 vs. 62.4 ± 12.3 years; $P < 0.001$; Table 1 and Fig. 1). A history of hypertension was more prevalent in women than in men (62.1 vs. 54.0%; $P < 0.001$). In contrast, current cigarette smoking was more common among men (44.8 vs. 31.4%; $P < 0.001$). The prevalences of diabetes mellitus, hyperlipidemia, obesity and known family history of CVD were similar in both groups (Table 1).

Previous medications including aspirin, clopidogrel, statin, beta-blocker and angiotensin-converting-enzyme (ACE)-inhibitor were similar in both groups (Table 1). Only diuretics, angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) were more often prescribed among women prior to the admission (Table 1).

At discharge, men were more likely prescribed statins (89.4 vs. 85.2%; $P = 0.004$) and ACE-inhibitor (67.0 vs. 56.8%; $P < 0.001$; Table 1). Conversely, women were more likely to be treated with clopidogrel (81.3 vs. 72.4%; $P < 0.001$), diuretics (26.5 vs. 20.0%; $P = 0.001$) and ARBs (15.7 vs. 10.5%; $P < 0.001$) (Table 1).

Hemodynamics and treatment strategy

By definition, all patients underwent coronary angiography. There was no significant difference noted in the use of vasopressors and intra-aortic balloon pump (IABP) between both groups (women vs. men: 6.2 vs. 7.3%, $P = 0.351$; 9.7 vs. 10.5%, $P = 0.55$, respectively). Resuscitation was similarly prevalent among both groups (women vs. men: 6.7 vs. 8.7%; $P = 0.12$). However, more men than women were intubated at the time of admission (8.5 vs. 5.7%; $P = 0.025$). LVEF was similar in both groups (women vs. men: 52.0 ± 11.9 vs. 52.9 ± 11.4%; $P = 0.22$). SBP and heart rate (HR) were significantly higher in women as compared with men (132.0 ± 27.8 vs. 124.6 ± 26.3 mmHg, $P < 0.001$; 75.7 ± 15.0 vs. 73.9 ± 15.1 b.p.m., $P = 0.002$).

Table 1 Baseline characteristics ($n = 2612$ patients)

	Total ($N = 2612$)	Men ($n = 2011$)	Women ($n = 601$)	*P*
Age	63.82 ± 12.50	62.40 ± 12.25	68.57 ± 12.19	<0.001
BMI	27.36 ± 8.55	27.52 ± 9.12	26.78 ± 6.00	0.001
ACS type				
STEMI	1371/2612 (52.5%)	1057/2011 (52.6%)	314/601 (52.2%)	0.89
NSTEMI	1011/2612 (38.7%)	777/2011 (38.6%)	234//601 (38.9%)	
Unstable angina	230//2612 (8.8%)	177//2011 (8.8%)	53//601 (8.8%)	
Cardiovascular risk factors				
HTN	1455/2604 (55.9%)	1083/2005 (54.0%)	372/599 (62.1%)	<0.001
DM	487/2604 (18.7%)	362/2005 (18.1%)	125/599 (20.9%)	0.12
Hyperlipidemia	1027/2604 (39.4%)	806/2005 (40.2%)	221/599 (36.9%)	0.15
Current smoker	1086/2604 (41.7%)	898/2005 (44.8%)	188/599 (31.4%)	<0.001
Obesity	550/2604 (21.1%)	416/2005 (20.7%)	134/599 (22.4%)	0.39
FH	678/2603 (26.0%)	514/2005 (25.6%)	164/598 (27.4%)	0.38
Medication on admission				
Aspirin	983//2596 (37.9%)	750//2000 (37.5%)	233//596 (39.1%)	0.48
Clopidogrel	371//2597 (14.3%)	280//2001 (14.0%)	91//596 (15.3%)	0.44
Statin	812//2596 (31.3%)	637//2001 (31.8%)	175//595 (29.4%)	0.26
Beta-blocker	746//2597 (28.7%)	570//2001 (28.5%)	176//596 (29.5%)	0.62
ACE-inhibitor	455//2597 (17.5%)	357//2001 (17.8%)	98//596 (16.4%)	0.43
Diuretics	496//2597 (19.1%)	354//2001 (17.7%)	142//596 (23.8%)	0.001
ARBS	376//2596 (14.5%)	266//2001 (13.3%)	110//595(18.5%)	0.002
CCBs	245//2597 (9.4%)	174//2001 (8.7%)	71//596 (11.9%)	0.018
Warfarin	92//2597 (3.5%)	69//2001 (3.4%)	23//596 (3.9%)	0.63
Medication at discharge				
Aspirin	2470//2607 (94.7%)	1907//2007 (95.0%)	563/601 (93.8%)	0.25
Clopidogrel	1940//2606 (74.4%)	1453//2007 (72.4%)	487//599 (81.3%)	<0.001
Statin	2306///2607 (88.5%)	1795//2007 (89.4%)	511//600 (85.2%)	0.004
Beta-blocker	1514//2607 (58.1%)	1170//2007 (58.3%)	344//600 (57.3%)	0.68
ACE-inhibitor	1685//2607 (64.6%)	1344//2007 (67.0%)	341//600 (56.8%)	<0.001
Diuretics	561//2605 (21.5%)	402//2006 (20.0%)	159//599 (26.5%)	0.001
ARBS	304//2604 (11.7%)	210//2005 (10.5%)	94//599 (15.7%)	<0.001
CCBs	181/2606 (6.9%)	142/2007 (7.1%)	39/599 (6.5%)	0.63
Warfarin	79/2606 (3.0%)	57/2007 (2.8%)	22/599 (3.7%)	0.30

ACE-inhibitor, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; DM, diabetes mellitus; FH, family history; HTN, hypertension; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Table 2 Baseline characteristics, (part 2)

	Total	Men	Women	*P*
Medication acutely				
Vasopressors	183/2611 (7.0%)	146/2010 (7.3%)	37/601 (6.2%)	0.35
GPIIb/IIIa	602/2606 (23.1%)	481/2005 (24.0%)	121/601 (20.1%)	0.049
Emergency procedures				
Intubation	204/2612 (7.8%)	170/2011 (8.5%)	34/601 (5.7%)	0.025
Resuscitation	214/2612 (8.2%)	174/2011 (8.7%)	40/601 (6.7%)	0.12
IABP	269/2612 (10.3%)	211/2011 (10.5%)	58/601 (9.7%)	0.55
Unstable	234/2611 (9.0%)	184/2010 (9.2%)	50/601 (8.3%)	0.53
Vital signs on admission (mean ± SD)				
HR (b.p.m.)	74.31 ± 15.11	73.88 ± 15.12	75.73 ± 15.03	0.002
SBP (mmHg)	126.31 ± 26.79	124.61 ± 26.26	131.99 ± 27.80	<0.001
DBP (mmHg)	70.01 ± 15.19	70.35 ± 15.04	68.00 ± 15.62	0.13
Hemodynamic parameters (mean ± SD)				
LVEDP (mmHg)	19.74 ± 8.30	19.64 ± 8.38	20.10 ± 8.02	0.23
LVEF (%)	52.66 ± 11.51	52.86 ± 11.40	51.96 ± 11.89	0.22
Location of the lesion				
LM	46/2611 (1.8%)	36/2011 (1.8%)	10/601 (1.7%)	0.84
LAD	1179/2611 (45.2%)	908/2011 (45.2%)	271/601 (45.1%)	0.98
LCX	506/2611 (19.4%)	394/2011 (19.6%)	112/601 (18.6%)	0.60
RCA	823/2611 (31.5%)	626/2011 (31.1%)	197/601 (32.8%)	0.45
Graft	56/2611 (2.1%)	45/2011 (2.2%)	11/601 (1.8%)	0.55
Coronary angiography findings				
Single-vessel disease	1069/2591 (41.3%)	799/2011 (39.7%)	270/601 (44.9%)	0.023
Multivessel disease	1522/2591 (58.7%)	1195/2011 (59.4%)	327/601 (54.4%)	0.029
Kind of intervention				
PCI	2410/2612 (92.2%)	1858/2011 (92.4%)	552/601 (91.8%)	0.66
CABG	96/2612 (3.7%)	79/2011 (3.9%)	17/601 (2.8%)	0.21
No intervention	106/2612 (4.1%)	74/2011 (3.7%)	32/601 (5.3%)	0.07

CABG, coronary artery bypass graft; GPIIb/IIIa, glycoprotein IIb/IIIa inhibitor; HR, heart rate; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RCA, right contrary artery.

Table 3 Laboratory values

	Total	Men	Women	*P*
Cholesterol (mmol/l)	4.81 (±1.22)	4.77 (±1.20)	4.95 (±1.26)	0.018
HDL (mmol/l)	1.13 (±.036)	1.08 (±.33)	1.29 (±0.41)	<0.001
LDL (mmol/l)	3.12 (±1.11)	3.11 (±1.09)	3.16 (±1.18)	0.80
TG (mmol/l)	1.39 (±1.01)	1.44 (±1.06)	1.20 (±0.75)	<0.001
CRP on ad (mg/l)	15.89 (±36.94)	15.33 (±36.67)	17.80 (±37.79)	<0.001
CRP max (mg/l)	58.32 (±90.15)	59.41 (±91.38)	54.67 (±85.84)	0.76
WBC on ad (g/l)	10.96 (±4.35)	11.05 (±4.35)	10.65 (±4.26)	0.043
WBC max (g/l)	12.53 (±5.43)	12.65 (±5.51)	12.10 (±5.13)	0.018
CK on ad (U/l)	600.84 (±1150.62)	615.99 (±1182.02)	546.06 (±1032.15)	0.08
CK max (U/l)	1619.57 (±2322.06)	1699.82 (±2449.35)	1343.51 (±1791.97)	0.008
CK-MB on ad (U/l)	80.94 (±131.25)	79.30 (±126.67)	86.68 (±146.07)	0.020
CK-MB max (U/l)	167.14 (±219.36)	166.79 (±223.91)	168.32 (±203.21)	0.61
Myoglobin on ad (μg/l)	525.66 (±1116.11)	542.40 (±1152.86)	467.99 (±977.86)	0.56
Myoglobin max (μg/l)	958.05 (±2145.17)	1020.99 (±2233.95)	863.22 (±1808.67)	0.08
Troponin-T on ad (μg/l)	1.22 (±3.46)	1.19 (±3.04)	1.33 (±4.64)	0.002
Troponin-T max (μg/l)	4.17 (±6.90)	4.17 (±6.85)	4.15 (±7.09)	0.62
NT-proBNP on ad (ng/l)	2068.88 (±5509.27)	1665.55 (±4800.64)	3456.19 (±7286.74)	<0.001
NT-proBNP max (ng/l)	3617.90 (±7639.52)	2986.53 (±6722.54)	5781.90 (±9880.35)	<0.001

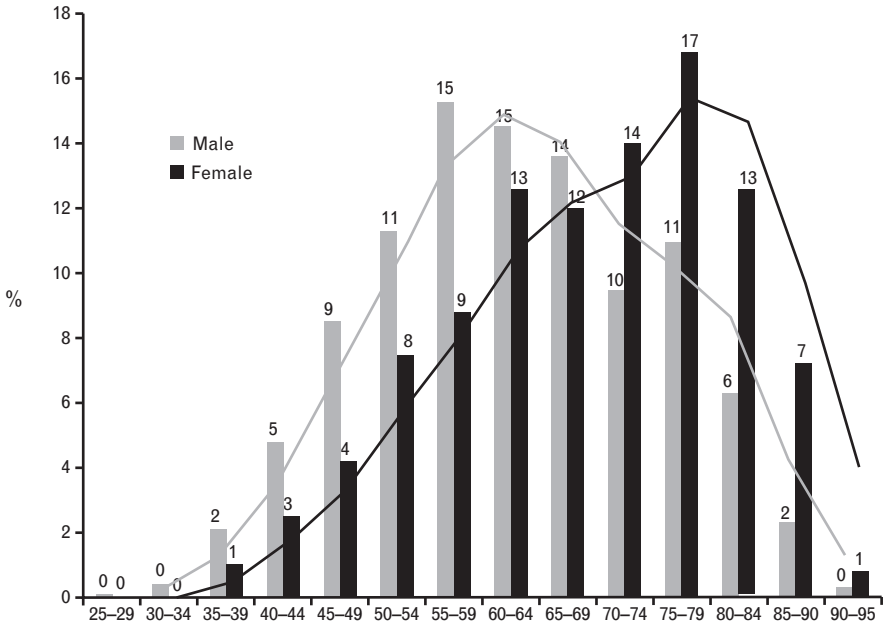
CK, creatine kinase; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; TG, triglyceride; WBC, white blood count.

Culprit lesions were assessed in the two groups (Table 2). SVD was less common in men than in women (39.7 vs. 44.9%; $P = 0.023$); conversely, MVD was more prevalent in men as compared with women (59.4 vs. 54.4%; $P = 0.029$). Lastly, glycoprotein IIb/IIIa antagonists (GPIIb/IIIa) were administered more frequently among men as compared with women (24.0 vs. 20.1%; $P = 0.049$).

Laboratory values

Troponin-T values on admission were higher in women than in men (1.33 ± 4.64 vs. 1.19 ± 3.04 μg/l; $P = 0.002$). However, no difference in peak values of troponin-T was noted during hospitalization (women vs. men: 4.15 ± 7.09 vs. 4.17 ± 6.85 μg/l; $P = 0.62$). N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) on admission and peak values were significantly higher in women as compared with men (3456.2 ± 7286.7 vs. 1665.6 ± 4800.6 ng/l, $P < 0.001$; 5781.9 ± 9880.4 vs. 2986.5 ± 6722.5 ng/l, $P < 0.001$, respectively). Also, high-density lipoprotein (HDL) cholesterol levels were significantly higher in women than in men (1.29 ± 0.41 vs. 1.08 ± 0.33 mmol/l; $P < 0.001$). However, low-density lipoprotein (LDL) levels were similar in both groups (3.16 ± 1.18 vs. 3.11 ± 1.09 mmol/l; $P = 0.80$). C-reactive

Fig. 1



Age distribution of men and women in acute coronary syndrome (ACS). Female patients were older than male patients at the time of diagnosis with ACS.

protein (CRP) levels on admission were significantly higher among women than among men (17.8 ± 37.8 vs. 15.3 ± 36.7 mg/l; $P < 0.001$); however, peak CRP levels did not differ (54.7 ± 85.8 vs. 59.4 ± 91.4 mg/l; $P = 0.76$). We did not find any differences between female and male patients either in BNP levels (women vs. men: 1811.1 ± 3932.6 vs. 1553.9 ± 5801.7 ng/l; $P = 0.16$) or in CRP levels on admission (women vs. men: 9.68 ± 28.1 vs. 7.03 ± 17.0 ng/l; $P = 0.72$). Laboratory values for both groups are shown in Table 3.

Follow-up data

The overall mortality rate was 4.86% and virtually similar in women and men (4.83 vs. 4.87%; $P = 0.96$). There were no significant differences for cardiovascular complications such as cardiogenic shock, tamponade, ventricle septum defect, stent thrombosis, myocardial infarction, repeat percutaneous coronary intervention (PCI), CABG and cerebrovascular accidents (Fig. 2).

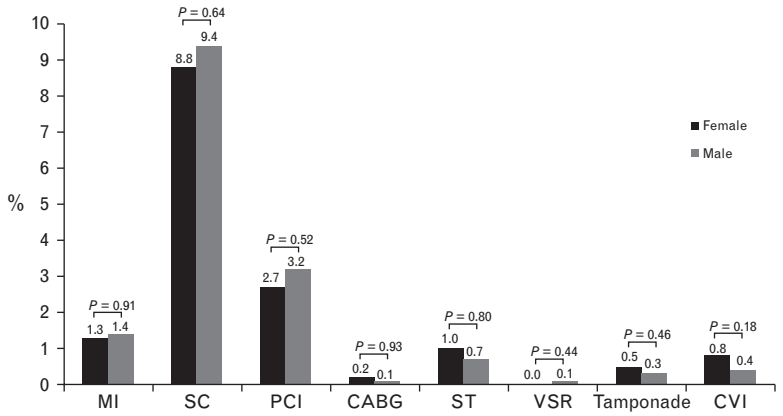
The Kaplan–Meier survival curve for 30 days' follow-up, including the combined endpoint of in-hospital death, nonfatal myocardial infarction, revascularization, CABG, stent thrombosis, as well as stroke, revealed no difference between men and women ($P = 0.98$) (Fig. 3).

Using univariate analysis, the following parameters emerged as predictors of MACCEs in female patients (Table 4): heart rate on admission, SBP on admission, maximal troponin, maximal creatine kinase (CK), maximal NT-proBNP and maximal CRP. Predictors of in-hospital death were (Table 5): heart rate, SBP on admission, maximal troponin, maximal CK, maximal NT-proBNP, maximal CRP and GPIIb/IIIa use. After adjustment for parameters entered into the multivariate model only maximal CK (OR 1.0, 95% CI 1.00–1.00, $P = 0.0056$) and peak levels of CRP (OR 1.00, 95% CI 1.00–1.01, $P = 0.0010$) remained significant independent predictors for MACCEs (Table 4). Strong independent predictors for in-hospital death were SBP (OR 0.96, 95% CI 0.93–0.98, $P = 0.0005$), maximal CRP (OR 1.01, 95% CI 1.00–1.01, $P = 0.044$) and GPIIb/IIIa use (OR 0.07, 95% CI 0.00–0.81, $P = 0.0295$) (Fig. 4, Table 5).

Discussion

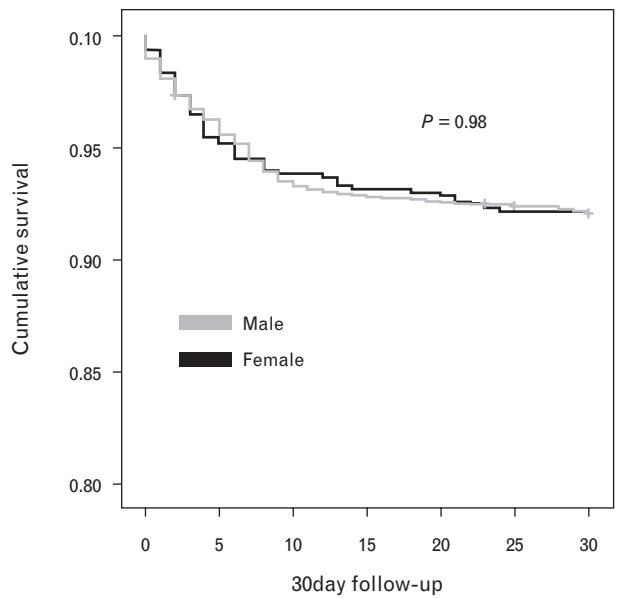
While for nearly two decades, disparities in the management and prevention of cardiovascular disease in women have been acknowledged,[15] very few RCTs adequately incorporated women.[16,17] Current guidelines are therefore often based primarily on information collected in men. This is of particular clinical importance as the clinical outcomes are far less favorable in women when compared with their male counterparts.[18,19] There is evidence that gender-related differences in the manifestation and presentation of cardiovascular disease exist. For instance, in ACS, women are less likely to present with classical angina symptoms.[20] In fact, most often, women with myocardial infarction will have acute respiratory and abdominal complaints as opposed to chest pain. Similarly, in stable CAD, diagnostic tests such as treadmill or bicycle exercise test are less sensitive and specific in women.[21] Therefore, it is plausible that ACS is both underdiagnosed and/or misdiagnosed in women, which in turn may explain the poor in-hospital outcomes, particularly in younger women.[22] Furthermore, medical and invasive treatment has been reported to be inferior in women.[23,24] Moreover, 30-day mortality in ACS has been found to be higher in women. In contrast, different studies demonstrated more favorable cardiac remodeling in elderly women and a better survival after myocardial infarction as compared with men. This has been elucidated by the protective estrogen regimen, different beta-adrenergic stimulation, renin–angiotensin system and greater resistance to apoptosis in women.[25]

Fig. 2



Comparison of cardiovascular complications (MI, myocardial infarction; SC, cardiogenic shock, PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ST, stent thrombosis, VSR, ventricle septum rupture, CVI, cerebrovascular insult) between female and male patients revealing no significant differences.

Fig. 3



Kaplan–Meier survival curve for short-term follow-up (30 days) in patients with acute coronary syndromes in women compared with men demonstrating no siginficant difference ($P = 0.98$).

Despite similar outcome measures, our results confirm the higher prevalence of MVD in male patients as compared with women presenting with ACS. The discrepancy in CAD extent between men and women has been already reported and is explained by the protective influence of estrogen regimen.[25] Although more women tend to have low-risk angiographic lesions, they continue to suffer more postintervention complications.[3,22,26]

Interestingly, previously reported data from Switzerland suggest that in-hospital mortality in STEMI patients might now be equivalent between the sexes.[27] Similarly, our single-center registry from 2007 to 2012 confirms that in-hospital death rate today is similar between men and women. This may be indicative of a closing gap in short-term outcomes possibly linked to the heightened awareness of cardiovascular disease in women. In addition, complications were equivalent amongst men and women. Also, treatment differences in the use of IABP and resuscitation were the same between the two groups, further highlighting a change in recent clinical treatment approach in women presenting with ACS.

Of note, acute treatment with GPIIb/IIIa inhibitors was substantially different between the sexes. There is evidence that GPIIb/IIIa inhibitors positively influence 30-day mortality and reduce target vessel revascularization (TVR). However, we did not observe a better outcome with GPIIb/IIIa use in our male population regarding TVR and in-hospital mortality rates, although according to guidelines, male patients were significantly more likely to be treated with GPIIb/IIIa inhibitors. Interestingly, in women, GPIIb/IIIa administration was a strong independent predictor of in-hospital death, but not MACCEs. Given that our observations were based on the current registry, further RCTs are needed to probe this hypothesis.

It is noteworthy that certain distinct characteristics were observed in the two groups. At the time of presentation, women were older and more likely to have hypertension, whereas men were more likely to be smokers. Interestingly, laboratory values on admission including troponin were significantly lower in female patients, whereas maximum troponin levels were similar. This is in line with previous studies. Such findings have raised concerns regarding the need for gender-specific cut-off levels, since thus far investigations have focused primarily on laboratory cut-off values primarily derived from male populations.[28] Plaque disturbances differ amongst men and women, which might at least in part explain differences in biomarker levels. Indeed in men, plaque ruptures appear more common, leading more often to complete coronary occlusion, whereas in women, plaque erosions are more often the culprit. Plaque rupture may serves as a strong impulse for recurrent thrombus embolization with high troponin release as compared with women.[29]

The fact that NT-proBNP was higher at baseline and peaked in women might be related to their higher age.

Table 4 Predictor of events on nominal logistic regression models (in female study population)

	MACCE ($n = 47$)			
	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Age	1.00 (0.98, 1.04)	0.32	1.02 (0.98, 1.0)	0.33
Heart rate	1.02 (0.99, 1.04)	0.06	0.98 (0.95, 1.01)	0.21
SBP on admission	0.96 (0.95, 0.98)	<0.0001	0.97 (0.95, 0.99)	0.0019
Troponin max	1.08 (1.05, 1.12)	<0.0001	1.01 (0.94, 1.08)	0.69
CK max	1.00 (1.00, 1.01)	<0.0001	1.00 (1.00, 1.00)	0.0056
NT-proBNP max	1.00 (1.00, 1.01)	<0.0001	1.00 (0.99, 1.00)	0.46
CRP max	1.007 (1.006, 1.008)	<0.0001	1.00 (1.00, 1.01)	0.001
Aspirin on admission	1.54 (0.83, 2.84)	0.17	2.85 (0.89, 9.52)	0.07
Statins on admission	1.41 (0.73, 2.65)	0.30	0.90 (0.27, 2.93)	0.87
GPIIb/IIIa	0.80 (0.34, 1.68)	0.57	0.45 (0.11, 1.52)	0.21

CI, confidence interval; CK, creatine kinase; CRP, C-reactive protein; GPIIb/IIIa, glyocoprotein IIb/IIIa inhibitor; MACCE, major adverse cardiac and cerebrovascular events; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; OR, odds ratio.

Table 5 Predictor of events on nominal logistic regression models (in female study population)

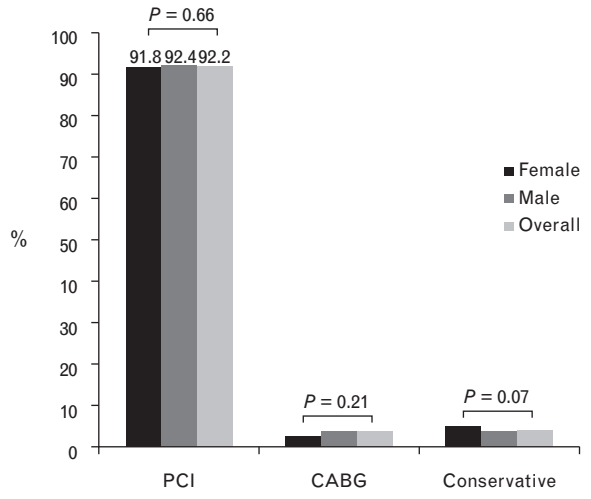
	All-cause death ($n = 29$)			
	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Age	1.01 (0.98, 1.04)	0.59	1.02 (0.95, 1.08)	0.55
Heart rate	1.03 (1.01, 1.06)	0.0099	0.99 (0.96, 1.03)	0.80
SBP on admission	0.95 (0.93, 0.96)	<0.0001	0.96 (0.93, 0.98)	0.0005
Troponin max	1.09 (1.05, 1.12)	<0.0001	1.03 (0.95, 1.11)	0.47
CK max	1.00 (1.00, 1.00)	<0.0001	1.00 (0.99, 1.00)	0.13
NT-proBNP max	1.00 (1.00, 1.00)	<0.0001	1.00 (0.99, 1.00)	0.22
CRP max	1.01 (1.00, 1.01)	<0.0001	1.01 (1.00, 1.01)	0.044
Aspirin on admission	0.77 (0.32, 1.70)	0.53	1.39 (0.27, 6.47)	0.68
Statins on admission	0.88 (0.34, 2.04)	0.77	0.51 (0.07, 3.14)	0.48
GPIIb/IIIa	0.28 (0.05, 0.96)	0.0415	0.07 (0.00, 0.81)	0.0295

CI, confidence interval; CK, creatine kinase; CRP, C-reactive protein; GPIIb/IIIa, glyocoprotein IIb/IIIa inhibitor; MACCE, major adverse cardiac and cerebrovascular events; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; OR, odds ratio.

Indeed, NT-proBNP levels increase with age.[30] As LVEF was similar in both groups, left ventricular dysfunction is unlikely to contribute to these findings. However, as long as the cut-off points for BNP and NT-proBNP are still under debate, the meaning of this finding remains an interesting observation with unclear clinical relevance.[28]

Furthermore, CRP levels at presentation were higher in female ACS patients, a finding also made by others.[31] This has been related to a more pronounced systemic inflammatory activation in female ACS patients compared with men.[28] However, recent investigations by other groups have failed to show an increase in other inflammation markers such as myeloperoxidase, CD-40 ligands or interleukin (IL)-10 in women.[32–34] Nevertheless, peak CRP levels emerged as an independent predictor for MACCEs and death in both men and women. Indeed, we previously found that NSTEMI, which present more commonly as heralded infarction, exhibit higher CRP values as they have already ongoing inflammation prior to presentation.[35]

Fig. 4



Distribution of revascularization, coronary artery bypass grafting and conservative therapy in female and male patients in acute coronary syndromes showing no difference in treatment strategy.

Furthermore, upon admission, certain medications such as CCBs, diuretics and ARBs were administered more frequently in women compared with men, most likely due to the higher prevalence of hypertension. Discharge medications also differed significantly, such that clopidogrel, diuretics and ARBs were administered significantly more in women. Conversely, statins, ACE-inhibitors and the new antiplatelet agents such as tigacrelor and prasugrel were more frequently administered in men at discharge.

In most studies published so far, women suffered a worse outcome after ACS. Amongst proposed factors are hormonal influences, the presence of more comorbidities and even psychosocial or economic differences between the two groups.

Moreover, drug response varies between the male and female gender, which can further add a layer of complexity in interpreting the outcomes. In contrast to previous registries, however, we remarkably found a similar short-term outcome between male and female patients with ACS. This strongly suggests that with early reperfusion using PCI and the use of modern adjunct pharmacotherapy, the gender gap can be closed in high-volume tertiary centers of high quality.

Small gender-specific differences, however, continue to exist, and medical management of female patients can improve further. For instance, our study revealed that treatment with statins as a part of the discharge medication regimen was slightly under-represented in women. Whereas the short-term outcomes are not affected, this might influence the long-term outcomes.

Thus, in summary, our study highlights that short-term outcome is similar between male and female patients presenting with ACS; therefore, the gender gap is closing. This improvement in women may be related to the finding that women and men received equally emergency treatment and PCI as our data show; however, gender

disparities in baseline characteristics exist and medical treatment is still different, and heightened awareness of this issue is a prerequisite among clinicians.

Acknowledgements

The study was supported in part by the Swiss National Research Foundation (Special Programme University Medicine Nr. 33CM30–124112/1) and unrestricted grants by Abbott Vascular and AstraZeneca (Baar, Switzerland), Biosensors (Morges, Switzerland), Eli Lilly (Geneve, Switzerland and Indianapolis, USA), Medtronic (Tollachenaz, Switzerland) and St. Jude (Brussels, Belgium). JRG has received a research grant ''Research Time'' from the University of Zurich.

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